Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1171–1174

TETRAHEDRON LETTERS

Isolation and structural analysis of novel conformational isomers of the *m*-xylylene-bridged calix[6]arenes: the 'partial cone' and 'inverted cone' isomers

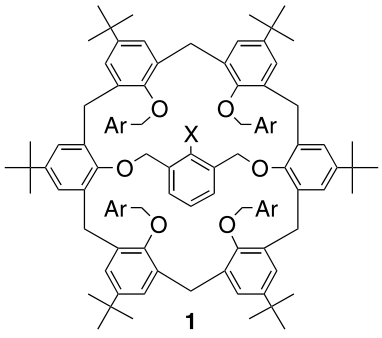
Shigehisa Akine,† Kei Goto* and Takayuki Kawashima*

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

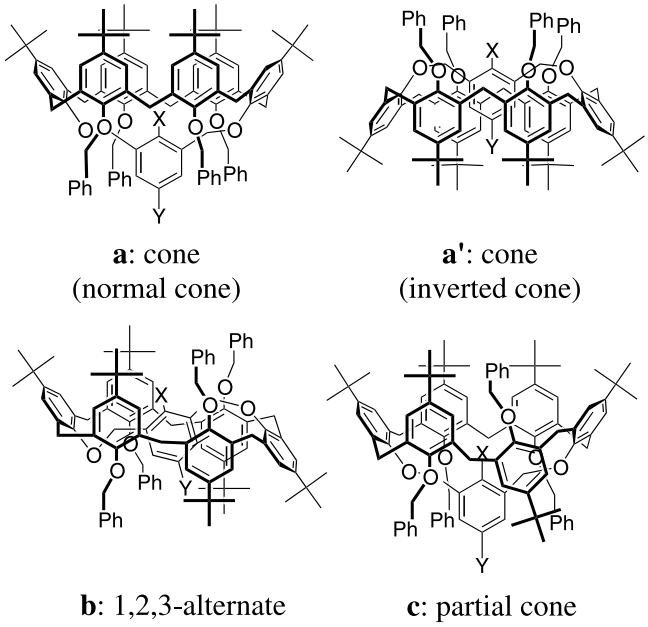
Received 11 November 2002; revised 12 December 2002; accepted 13 December 2002

Abstract—In the benzylation of a *m*-xylylene-bridged calix[6]arene tetrol, the first example of the 'partial cone' isomer of a calix[6]arene was obtained in addition to the corresponding cone and 1,2,3-alternate isomers, and its structure was established by X-ray crystallographic analysis. The synthesis and crystal structure of the 'inverted cone' isomer as well as its thermal conversion to the 'normal cone' isomer are also described. © 2003 Elsevier Science Ltd. All rights reserved.

Whereas the conformation of calix[4]arenes can be easily immobilized by functionalization at the lower rim to form four conformational isomers (cone, partial cone, 1,2-alternate, and 1,3-alternate),[1,2] it has been very difficult to fix the conformation of calix[6]arenes despite a large demand for their structurally well-defined derivatives.[1,3–8] Although some examples of calix[6]arenes fixed in one conformation were reported,[9–12] there have been only a few examples of isolation of the plural conformational isomers of calix[6]arenes.[13–18] We previously succeeded in the isolation of the cone and 1,2,3-alternate isomers of the bridged calix[6]arenes represented by general formula **1** (Schemes 1 and 2).[14–16,18] It was found that the cone isomer and the 1,2,3-alternate isomer are different from each other in many properties such as the reactivity of



Scheme 1.



Scheme 2.

Keywords: calixarene; conformational isomer; X-ray crystal structure; isomerization.

* Corresponding authors. Tel.: +81-3-5800-6899; fax: +81-3-5800-6899; e-mail: goto@chem.s.u-tokyo.ac.jp; takayuki@chem.s.u-tokyo.ac.jp

† Present address: Department of Chemistry, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan.

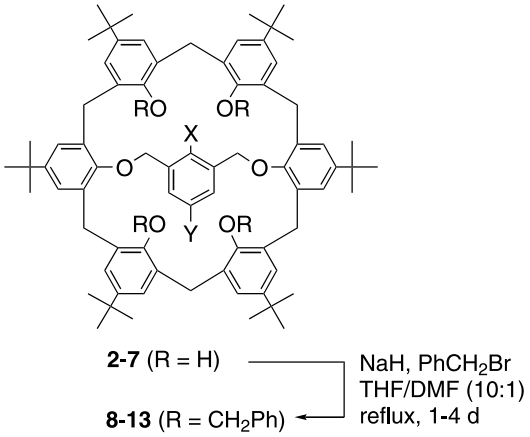
PII: S0040-4039(02)02833-2

the intracavity functional group,[18] the critical micelle concentration of the water-soluble derivatives,[15] etc. For the bridged calix[6]arenes of type **1**, there should be other possible conformational isomers not yet found, in addition to the cone and 1,2,3-alternate isomers.[19] If a wider variety of the conformational isomers of calix[6]arenes are obtained, it will increase their utility as a molecular platform. In this communication, we report the synthesis and crystal structures of novel conformational isomers, the 'partial cone' and 'inverted cone' isomers (Scheme 2), of this type of bridged calix[6]arenes.[20]

We previously reported that the benzylation of the tetrahydroxy compound **2**[21] in the presence of NaH afforded the cone and 1,2,3-alternate isomers **8a** and **8b** of the tetrabenzylated product in 58 and 16% yields, respectively (Table 1, entry 1).[14] In these benzylated compounds, the flipping motions of the four non-bridgehead aromatic rings of the calix[6]arene macrocycle are restricted on the laboratory time-scale, and neither interconversion between the cone and 1,2,3-alternate isomers nor conversion to other isomers was observed even after heating either of them at 120°C for 24 h.

When the tetrahydroxy compound **3** bearing a methoxy functionality on the bridging unit was benzylated under similar conditions, the third conformational isomer **9c**‡ was obtained in addition to the corresponding cone and 1,2,3-alternate isomers **9a** and **9b** (Table 1, entry 2). These three isomers were separated by silica gel chromatography. The ^{1}H NMR spectrum of **9c** showed six *tert*-butyl resonances (1:1:1:1:1:1 ratio), six pairs of doublets (1:1:1:1:1:1 ratio) for $ArCH_2Ar$ methylene groups, and six pairs of doublets (1:1:1:1:1:1 ratio) for $ArCH_2O$ methylenes (two methylene groups of the bridging unit and four $PhCH_2O$ methylenes at the lower rim). This spectral pattern is indicative of C_1 symmetry of the molecule and completely different from those of **9a** and **9b** bearing C_{2v} and C_s symmetry, respectively. The structure of **9c** was finally established by X-ray crystallographic analysis, as shown in Figure 1.§ The calix[6]arene moiety adopts the conformation where only one of the six aromatic rings is oriented downward while the others upward. This conformation corresponds to the partial cone conformation of calix[4]arenes, where three rings are directed upward and only one downward. In the previous report,[22] we predicted the existence of the 'partial cone' isomer for

Table 1. Results of benzylation of bridged calix[6]arenes **2**–**7**



Entry	S.M.	X	Y	Product	Yield[a]			
					a	**a′**	**b**	**c**
1[b]	**2**	Br	H	**8**	58	0	16	0
2	**3**	OMe	Br	**9**	35	0	7	7
3	**4**	H	H	**10**	63	0	1	6
4	**5**	H	Br	**11**	52	0	0	4
5[c]	**6**	SeBu^n	H	**12**	0	59	4	0
6	**7**	C≡CPh	H	**13**	0	15	12	0

[a] Isolated yield.
[b] Ref. 14.
[c] Ref. 18.

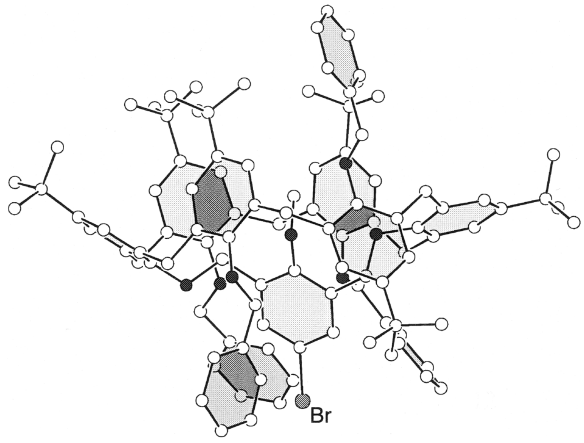
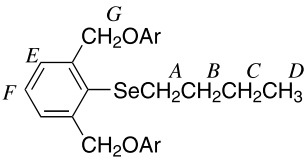


Figure 1. Crystal structure of the 'partial cone' isomer **9c**. One of the two independent molecules is shown.

‡ **9c**: colorless crystals, mp 269–272°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.62 (s, 9H), 0.77 (s, 9H), 0.98 (s, 9H), 1.14 (s, 9H), 1.35 (s, 9H), 1.39 (s, 9H), 1.40 (s, 3H), 2.93 (d, J=14.2 Hz, 1H), 3.12 (d, J=14.0 Hz, 1H), 3.14 (d, J=16.2 Hz, 1H), 3.34 (d, J=12.5 Hz, 1H), 3.36 (d, J=12.1 Hz, 1H), 3.37 (d, J=12.1 Hz, 1H), 3.39 (d, J=16.3 Hz, 1H), 3.63 (d, J=15.7 Hz, 1H), 3.69 (d, J=12.5 Hz, 1H), 3.89 (d, J=13.5 Hz, 1H), 4.02 (d, J=13.5 Hz, 1H), 4.10 (d, J=13.1 Hz, 1H), 4.13 (d, J=13.1 Hz, 1H), 4.19 (d, J=16.2 Hz, 1H), 4.21 (d, J=16.3 Hz, 1H), 4.30 (d, J=14.2 Hz, 1H), 4.47 (d, J=15.7 Hz, 1H), 4.62 (s, 2H), 4.65 (d, J=11.7 Hz, 1H), 4.67 (d, J=14.0 Hz, 1H), 4.76 (d, J=11.7 Hz, 1H), 4.81 (d, J=11.6 Hz, 1H), 4.91 (d, J=11.6 Hz, 1H), 6.16 (d, J=1.4 Hz, 1H), 6.47 (d, J=1.9 Hz, 1H), 6.90 (d, J=7.4 Hz, 2H), 6.99 (d, J=2.0 Hz, 1H), 6.99 (d, J=2.1 Hz, 1H), 7.04 (d, J=2.1 Hz, 1H), 7.05 (d, J=2.2 Hz, 1H), 7.14–7.16 (m, 4H), 7.21–7.24 (m, 7H), 7.27–7.38 (m, 12H), 7.42–7.44 (m, 2H), 7.75 (d, J=2.2 Hz, 1H). Anal. calcd for $C_{103}H_{115}BrO_7 \cdot H_2O$: C, 79.15; H, 7.54; Br, 5.11. Found: C, 79.34; H, 7.51; Br, 5.58%.

§ Crystallographic data for the 'partial cone' isomer **9c**: $C_{103}H_{115}BrO_7$, triclinic, P–1, a=14.117(2), b=25.303(3), c=25.117(3) Å, α=88.139(5), β=83.716(6), γ=75.785(5)°, V=8645(2) Å^3, Z=4, D_{calcd}=1.187 g/cm^3, T=120 K, collected reflections, 49419, unique=27325 (R_{int}=0.062), R_1=0.0991 ($I>2\sigma(I)$), wR_2=0.2424 (all data).[24]

Table 2. Selected ^{1}H NMR chemical shifts of butyl selenides **12a** and **12a′**[a]



Compound	A	B	C	D	E	F	G
12a	0.26	−0.55	−0.79	−0.70	7.31	6.82	4.45
12a′	2.75	1.35	1.10	0.77	3.88	4.48	4.83

[a] Measured in $CDCl_3$ at 500 MHz. Assignments were based on 2D COSY.

the derivative of **9** bearing four ethoxy groups at the lower rim based on molecular mechanics calculations. Although partial cone isomers are familiar in the case of calix[4]arenes, this is the first example of the isolation and crystallographic analysis of the 'partial cone' isomer of a calix[6]arene. The downward-oriented aromatic ring is inclined inward whereas the bridgehead ring adjacent to it leans outward. According to the notation introduced by Gutche et al.,[23] this conformation can be designated as (**uo**,di,u,u,u,u). The isomers with the same spectral pattern were also obtained in the benzylation of the tetrahydroxy compounds **4** and **5** (Table 1, entries 3 and 4). These isomers **10c** and **11c** are also considered to adopt the 'partial cone' conformation. It is notable that these 'partial cone' isomers have molecular asymmetry based on conformation of the calix[6]arene macrocycle. Such inherently chiral calix[6]arenes are expected to serve as a chiral reaction environment for the intracavity functional group as well as a basic framework of chiral receptors.

Recently, we reported the synthesis of the cone and 1,2,3-alternate isomers of the tetrabenzyloxy compound **12** bearing a butylseleno group (Table 1, entry 5) although the structure of the cone isomer was not definitely determined.[18] In the ^{1}H NMR spectrum of the cone isomer of **12** obtained there, the aromatic protons of the bridging unit appeared at very high fields (δ 3.88 and 4.48; Table 2, lower row), suggesting that it has the 'inverted cone' conformation **a′** (Scheme 2), where these protons are highly shielded by the calixarene aromatic rings, rather than the 'normal cone' conformation **a**, where the butylseleno group is in the cavity. X-Ray crystallographic analysis established its 'inverted cone' structure, where the butylseleno group is directed outward of the cavity (Fig. 2(a)).¶ It is notable that, upon heating in toluene-d_8 at 110°C for one month, the 'inverted cone' isomer **12a′** was converted to the 'normal cone' isomer **12a** quantitatively (Scheme 3). In the ^{1}H NMR spectrum of **12a**, the aromatic protons of the bridging unit appeared at a normal region, whereas the protons of the butyl group resonated at fairly high fields (Table 2, upper row). The normal cone conformation of **12a** was also confirmed by X-ray analysis (Fig. 2(b)).‖

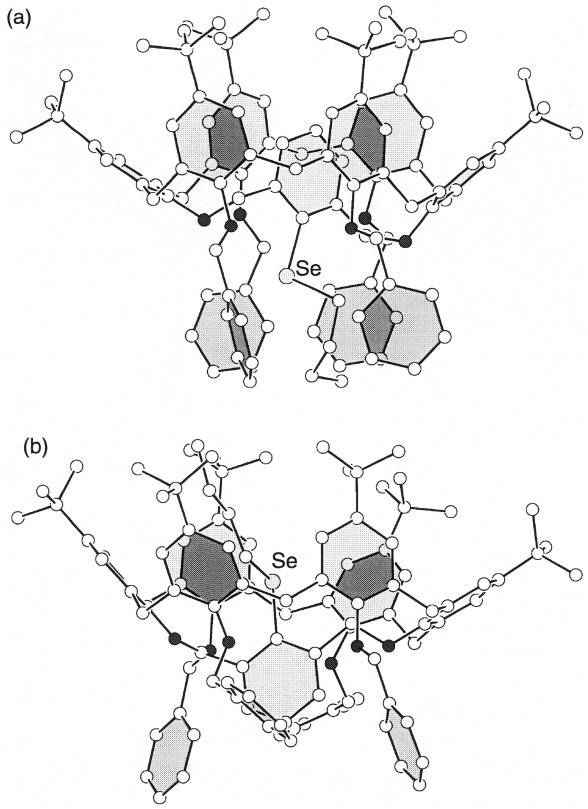
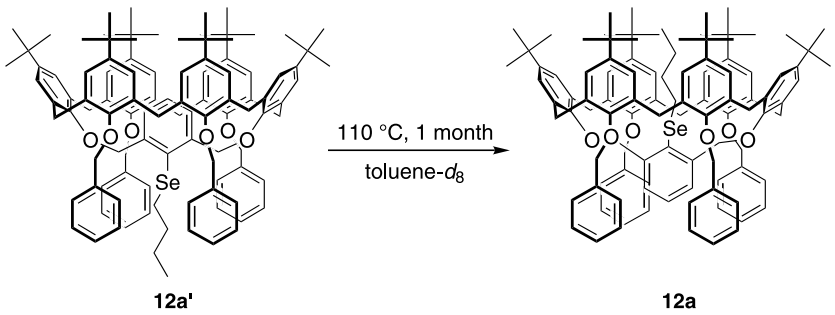


Figure 2. Crystal structures of two cone isomers of butyl selenide **12**. (a) 'Inverted cone' isomer **12a′** and (b) 'normal cone' isomer **12a**.

¶ Crystallographic data for the 'inverted cone' isomer **12a′**: $C_{106}H_{122}O_6Se$, monoclinic, $P2_1/c$, $a=14.320(1)$, $b=23.903(1)$, $c=25.856(1)$ Å, $\beta=97.128(2)°$, $V=8781.9(8)$ Å^3, $Z=4$, $D_{calcd}=1.188$ g/cm^3, $T=120$ K, collected reflections, 57351, unique = 16450 ($R_{int}=0.031$), $R_1=0.0485$ ($I>2\sigma(I)$), $wR_2=0.1263$ (all data).[24]

‖ Crystallographic data for the 'normal cone' isomer **12a**: $C_{106}H_{122}O_6Se$: triclinic, $P\bar{1}$, $a=16.037(1)$, $b=17.802(1)$, $c=18.099(1)$ Å, $\alpha=67.933(2)$, $\beta=81.442(2)$, $\gamma=67.582(2)°$, $V=4426.6(3)$ Å^3, $Z=2$, $D_{calcd}=1.179$ g/cm^3, $T=120$ K, collected reflections, 30485, unique = 15575 ($R_{int}=0.014$), $R_1=0.0487$ ($I>2\sigma(I)$), $wR_2=0.1318$ (all data).[24]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 196819 (**9c**), 196820 (**12a′**), and 196821 (**12a**).



Scheme 3.

These results indicate that the 'inverted cone' isomer **12a**′ is the kinetic product and, by prolonged heating, it was slowly converted to the 'normal cone' isomer **12a**, which is thermodynamically more stable. This conversion is considered to be caused by the inversion of the bridging aromatic ring with the cone conformation of the calix[6]arene macrocycle being retained. Formation of the 'inverted cone' isomer was also observed in the benzylation of the tetrahydroxy compound **7** bearing a phenylethynyl group on the bridge, where isomer **13a**′ was obtained in addition to the 1,2,3-alternate isomer **13b** (Table 1, entry 6). When the bridging unit has a sterically demanding functionality on it, the formation of the 'inverted cone' isomer is considered to be kinetically favored, although the 'normal cone' isomer is thermodynamically more stable as demonstrated by the conversion of **12a**′ to **12a**.

In summary, we have succeeded in the first synthesis and structural analysis of a calix[6]arene fixed in the 'partial cone' conformation. The crystal structure of the 'inverted cone' isomer and its conversion to the 'normal cone' isomer were also presented.

References

1. For comprehensive reviews on calixarenes, see: (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; (b) *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer: Dordrecht, 2001.
2. Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409–426.
3. Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6059–6063.
4. Casnati, A.; Minari, P.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 1413–1414.
5. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160–3166.
6. Otsuka, H.; Araki, K.; Sakaki, T.; Nakashima, K.; Shinkai, S. *Tetrahedron Lett.* **1993**, *34*, 7275–7278.
7. Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1994**, *59*, 3871–3879.
8. van Duynhoven, J. P. M.; Janssen, R. G.; Verboom, W.; Franken, S. M.; Casnati, A.; Pochini, A.; Ungaro, R.; de Mendoza, J.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1994**, *116*, 5814–5822.
9. Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251–1254.
10. Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032–4034.
11. Otsuka, H.; Araki, K.; Matsumoto, H.; Harada, T.; Shinkai, S. *J. Org. Chem.* **1995**, *60*, 4862–4867.
12. Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271–4275.
13. Neri, P.; Rocco, C.; Consoli, G. M. L.; Piattelli, M. *J. Org. Chem.* **1993**, *58*, 6535–6537.
14. Saiki, T.; Goto, K.; Okazaki, R. *Chem. Lett.* **1996**, 993–994.
15. Akine, S.; Goto, K.; Kawashima, T.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2781–2783.
16. Akine, S.; Goto, K.; Kawashima, T. *J. Inclusion Phenom. Macrocycl. Chem.* **2000**, *36*, 119–124.
17. Blanda, M. T.; Farmer, D. B.; Brodbelt, J. S.; Goolsby, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 1486–1491.
18. Goto, K.; Saiki, T.; Akine, S.; Kawashima, T.; Okazaki, R. *Heteroatom Chem.* **2001**, *12*, 195–197.
19. Lüning et al. reported that the benzylation of a pyridine-bridged calix[6]arene afforded a tetrabenzylated compound with the conformation of flattened (**u**,u,d,u,u,d) conformation in 7% yield. Its structure was, however, not sufficiently elucidated. See: Ross, H.; Lüning, U. *Liebigs Ann.* **1996**, 1367–1373.
20. A part of this work has been presented in 5th International Conference on Calixarene Chemistry, Perth, Australia, Sept. 19–23, 1999, L-31.
21. Saiki, T.; Akine, S.; Goto, K.; Tokitoh, N.; Kawashima, T.; Okazaki, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1893–1902.
22. Akine, S.; Goto, K.; Kawashima, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2167–2174.
23. Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572–6579.
24. Sheldrick, G. M. SHELXL-97. Program for crystal structure refinement, University of Göttingen, 1997.